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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/214,009	05/07/99	BEEKMAN N	3898US

HM12/1023

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 10/23/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/214,009	Johannes et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 30, 2001*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above, claim(s) *7, 8, and 11* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6, 9, 10, and 12-23* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *6.*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Applicants' Amendments

1) Acknowledgment is made of Applicants' preliminary amendments filed 12/23/98 (paper no. 5), 12/14/99 (paper no. 8) and 07/30/01 (paper no. 15). With these, Applicants have amended the specification.

Election

2) Acknowledgment is made of Applicants' election filed 01/23/01 (paper no. 12) of invention I, claims 6 and 21, to the extent these claims encompass SEQ ID NO: 1, in response to the restriction requirement mailed 07/05/00 (paper no. 9). Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P § 818.03(a)).

Status of Claims

3) Claims 3, 5-9, 11, 12, 15, 18, 21 and 22 have been amended via the preliminary amendment filed 12/23/98.

Claims 1-23 are pending.

Claims 6 and 21, with respect to SEQ ID NO: 1, are elected. The linking claims 1-5, 9, 10, 12-20, 22 and 23, to the extent these claims encompass SEQ ID NO: 1, are joined with the elected claims.

Claims 7, 8 and 11 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

The elected claims 1-6, 9, 10 and 12-23, to the extent these claims encompass SEQ ID NO: 1, are under examination. An Action on the Merits for these claims is issued.

Information Disclosure Statement

4) Acknowledgment is made of Applicants' information disclosure statement filed 12/23/98 (paper no. 6). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 17).

Sequence Listing

5) Acknowledgment is made of Applicants' CRF/sequence, which has been entered in the

case on 01/04/00.

Drawings

6) This application has been filed with an informal drawing which is acceptable for examination purposes only. Formal drawing will be required when the application is allowed.

Priority

7) This application is filed under 35 U.S.C. 371 of application PCT/NL97/00354, filed 06/24/97, which claims priority to application, 96201766.1, filed 06/25/96 in Europe. It is noted that a certified copy of the priority application 96201766.1 has been made of record.

Abstract

8) This application currently does not contain an abstract of the disclosure as required by 37 C.F.R 1.72(b). However, as this application is filed under 371 with priority to PCT/NL97/00354, a copy of the published abstract from PCT/NL97/00354 is placed in the instant application as page number 30. If Applicants desired changes to the abstract, such changes should be directed to the abstract of the PCT/NL97/00354.

Specification - Informalities

9) The instant application is informal in the format or arrangement of the specification. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the Applicants' use.

Content of Specification

(a) Title of the Invention: See 37 C.F.R 1.72(a). The title of the invention should be placed at the top of the first page of the specification. It should be brief but technically accurate and descriptive, preferably from two to seven words.

(b) Cross-References to Related Applications: See 37 C.F.R 1.78 and M.P.E.P § 201.11.

(c) Statement Regarding Federally Sponsored Research and Development: See M.P.E.P § 310.

(d) Reference to a "Microfiche Appendix": See 37 C.F.R 1.96(c) and M.P.E.P § 608.05. The total number of microfiche and the total number frames should be specified.

(e) Background of the Invention: The specification should set forth the Background of the Invention in two parts:

(1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the

applicable U.S. patent classification definitions of the subject matter of the claimed invention. This item may also be titled "Technical Field."

(2) Description of the Related Art: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art."

(f) Brief Summary of the Invention: A brief summary or general statement of the invention as set forth in 37 C.F.R 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in the Background of the Invention). In chemical cases it should point out in general terms the utility of the invention. If possible, the nature and gist of the invention or the inventive concept should be set forth. Objects of the invention should be treated briefly and only to the extent that they contribute to an understanding of the invention.

(g) Brief Description of the Several Views of the Drawing(s): A reference to and brief description of the drawing(s) as set forth in 37 C.F.R 1.74.

(h) Detailed Description of the Invention: A description of the preferred embodiment(s) of the invention as required in 37 C.F.R 1.71. The description should be as short and specific as is necessary to describe the invention adequately and accurately. This item may also be titled "Best Mode for Carrying Out the Invention." Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail. However, where particularly complicated subject matter is involved or where the elements, compounds, or processes may not be commonly or widely known in the field, the specification should refer to another patent or readily available publication which adequately describes the subject matter.

(i) Claim or Claims: See 37 C.F.R 1.75 and M.P.E.P § 608.01(m). The claim or claims must commence on separate sheet. (37 C.F.R 1.52(b)). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. There may be plural indentations to further segregate subcombinations or related steps.

(j) Abstract of the Disclosure: A brief narrative of the disclosure as a whole in a single paragraph of 250 words or less on a separate sheet following the claims.

(k) Drawings: See 37 C.F.R 1.81, 1.83-1.85, and M.P.E.P § 608.02.

(l) Sequence Listing: See 37 C.F.R 1.821-1.825.

The instant specification is further objected to because of the reasons given below:

(i) The first paragraph of the specification does not provide information on the

priority application(s).

(ii) Certain terms are misspelled. For instance, 'ovalbumine' on page 2, line14;

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

10) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

11) Claims 1-6, 9, 10 and 12 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is vague and indefinite in the recitation "certain" physiological conditions (see last two lines), because it is unclear what is encompassed in this limitation.

(b) Claim 2 is vague and confusing in the recitation "the vaccine or preparation". It is unclear what the differences are, if any, between the 'vaccine' and the 'preparation'.

(c) Claim 2 is vague and/or incomplete in the recitation "has been administered", because it is unclear to whom or to what subject the vaccine is administered.

(d) Claim 6 is vague in the recitation "peptide consisting essentially of the amino acid sequence of SEQ ID NO. 1", because it is unclear what amino acid residues are encompassed in the peptide. It is unclear whether Applicants intend an open or closed language by the recitation "peptide consisting essentially of". It is not clear what else is contained in the recited peptide other than the 20 amino acid residues contained in SEQ ID NO: 1.

(e) Claims 2-6, 9, 10 and 12, which depend directly or indirectly from claim 1, are also rejected as being indefinite because of the vagueness or indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C § 102

12) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> **(e)** The invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

> has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

13) Claims 1-4, 12, 13, 19, 22 and 23 are rejected under 35 U.S.C § 102(b) as being anticipated by Yatvin *et al.* (US 5,256,641 - Applicants' IDS).

Yatvin *et al.* disclose an antigenically-active peptide covalently linked to a lipid via a thioester bond, which would facilitate the release of the peptide at the target site (see first full paragraph in column 8) and therefore, is labile. A method of preparing the conjugate is taught (see abstract and Example 7). The peptide is chemically synthesized (see column 7, lines 2-4). A fatty acid is used in the conjugate (see Example 7). The conjugate is used as a vaccine (see last paragraph in column 10). The vaccine or the composition comprising the conjugate and a pharmaceutically acceptable carrier is administered to vertebrate animals (see second and fifth full paragraphs in column 6; and first full paragraph in column 5).

Claims 1-4, 12, 13, 19, 22 and 23 are anticipated by Yatvin *et al.*

Rejection(s) under 35 U.S.C. § 103

14) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

15) Claims 1, 5, 13, 14, 19 and 20 are rejected under 35 U.S.C § 103(a) as being unpatentable over Yatvin *et al.* (US 5,256,641 - Applicants' IDS) or Haynes *et al.* (US 5,013,548) in view of Wiedemann *et al.* (*J. Pathol.* 164: 265-271, 1991).

The teachings of Yatvin *et al.* are explained above.

Haynes *et al.* disclose vaccines or immunogenic preparations comprising a synthetic antigenic determinant peptide of HIV, linked directly or indirectly, to a protein carrier molecule suitable for vaccination via a disulfide bond and a method of making the same (see abstract; first paragraph under 'Summary of Invention' and 'Detailed Description of the Invention'; first full paragraph in column 7; and first paragraph in column 5). The coupling agent used in conjugation is M-maleimidobenzoyl-N-hydroxysuccinimide ester or MBS (see second paragraph in column 5). The vaccine is administered with a pharmaceutically acceptable carrier and an adjuvant (see last paragraph in column 4). That the prior art vaccine contains a labile bond due to the use of the MBS linker is implicit from the teachings of Haynes *et al.*

Yatvin *et al.* or Haynes *et al.* do not disclose the use of palmitic acid carrier in their conjugate vaccine or composition.

However, the use of palmitic acid residues in a conjugate vaccine or composition is conventional and routine in the art. For instance, Wiedemann *et al.* teach the use of P_3CS or N-palmitoyl-S-(2,3-bis(palmitoyl)-(2RS)-propyl)-(R)-cysteinyl-(S)-serine for coupling synthetic peptide antigens. The advantage of using such a substance in a conjugate is taught to be that P_3CS not only acts as an immunogen, but as a built-in adjuvant (see summary and page 265). Such a single conjugate vaccine has the advantage of being administered without any additional adjuvant or carrier (see paragraph bridging pages 265 and 266).

Given the conventional use of P_3CS as a carrier in peptide conjugates, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Yatvin's generic fatty acid or Haynes' protein carrier molecule with Wiedemann specific P_3CS adjuvantic carrier to produce the vaccine or composition of the instant invention, with a reasonable expectation of success. A skilled artisan would have been motivated to produce the instant invention for the expected benefit of providing the advantageous function of built-in adjuvanticity to the prior art peptide-containing or antigen-containing conjugate in addition to providing carrier functions, as taught by Wiedemann *et al.*

Claims 1, 5, 13, 14, 19 and 20 are *prima facie* obvious over the prior art of record.

16) Claims 1-6, 9, 10 and 12-23 are rejected under 35 U.S.C § 103(a) as being unpatentable

over Meleon *et al.* (US 6,284,733) in view of Wiedemann *et al.* (*J. Pathol.* 164: 265-271, 1991).

The reference of Meleon *et al.* ('733) is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C § 102 and accordingly is not disqualified under U.S.C 103(a).

Meleon *et al.* ('733) teach a LHRH or GnRH petide linked to a carrier and a vaccine comprising the same (see abstract). The peptide has the aminoacid sequence of SEQ ID NO: 1 and is present as a monomer or a dimer (see columns 6 and 9; and claims). The LHRH coupled to a carrier is present in Freund's complete adjuvant (see column 3, lines 30 and 31; Example 2; and column 8, lines 17-21). Administration of the vaccine in Freund's complete adjuvant elicits unwanted side effects such as development of chronic inflammatory reactions, pain and abscess formation (see column 4, third full paragraph). A peptide composition consisting of two or dimerized LHRH sequences in tandem can be coupled to a carrier compound. The linking is accomplished via a disulfide bridge (i.e., bond). The dimerized peptide (i.e., the two copies of the sequences) is then conjugated to a carrier compound (see third full paragraph in column 5; paragraph bridging column 5 and 6; Example 2; and last paragraph in column 6).

Meleon *et al.* ('733) do not teach the LHRH-LHRH (SEQ ID NO: 1) dipeptide linked directly or indirectly to a fatty acid or palmitic acid carrier.

However, the use of palmitic acid in a conjugate vaccine or composition is conventional and routine in the art. For instance, Wiedemann *et al.* teach the use of P_3CS or N-palmitoyl-S-(2,3-bis(palmitoyl)-(2RS)-propyl)-(R)-cysteinyl-(S)-serine for coupling synthetic peptide antigens. The advantage of using such a substance in a conjugate is taught to be that P_3CS not only acts as an immunogen, but as a built-in adjuvant (see summary and page 265). Such a single conjugate vaccine has the advantage of being administered without any additional adjuvant or carrier (see paragraph bridging pages 265 and 266).

Given the conventional use of P_3CS as a carrier in peptide conjugates, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Meleon's carrier molecule with Wiedemann specific P_3CS adjuvantic carrier to produce the vaccine or composition of the instant invention, with a reasonable expectation of success. A skilled artisan would have been motivated to produce the instant invention for the expected

benefit of providing the advantageous function of built-in adjuvanticity to the prior art LHRH dimer-containing conjugate in addition to providing carrier functions, as taught by Wiedemann *et al.* A skilled artisan would have been motivated to produce the instant invention for the purpose of eliminating the use of the Freund's complete adjuvant in Meleons' vaccine or composition by having Wiedemann's P_3CS adjuvant instead, in order to avoid the unpleasant side effects of Freund's complete adjuvant taught by Meleon *et al.* ('733).

Claims 1-6, 9, 10 and 12-23 are *prima facie* obvious over the prior art of record.

Objection(s)

17) Claims 1, 6, 12, 15, 18, 19, 21 and 23 are objected to for the following reasons:

(a) Claims 12 and 23 are objected to for the recitation "with pharmaceutically acceptable carrier" without a preceding article. It is suggested that Applicants replace the recitation with --with a pharmaceutically acceptable carrier--.

(b) For clarity, in claims 1 and 19, it is suggested that Applicants replace the recitation "fatty acid peptide carrier" with the recitation --fatty acid-peptide carrier--.

(c) In claims 6, 15, 18 and 21, for clarity and to be correct, it is suggested that Applicants replace the recitation "SEQ. I.D." with --SEQ ID--.

(d) Claims 15, 18 and 20 are objected for including non-elected subject matter, i.e., non-elected peptide sequences.

Remarks

18) Claims 1-6, 9, 10 and 12-23 stand rejected.

19) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicant's disclosure:

- Stein *et al.* (US 6,258,774) disclose therapeutic compositions comprising a peptide conjugated to a carrier via a disulfide bond which gets broken *in vivo* in a physiologically relevant reducing environment (see entire document).

20) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone

number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week.

21) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

October 2001

S. DEVI, PH.D.
PRIMARY EXAMINER